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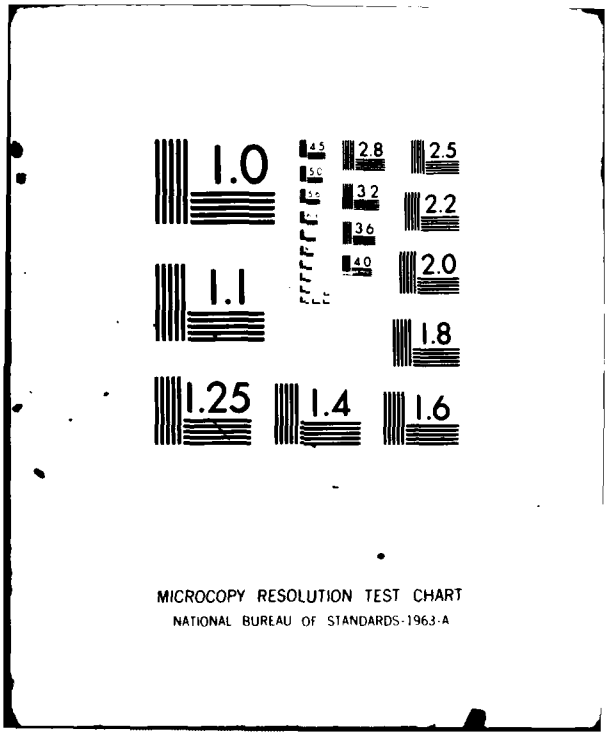
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TECHNICAL REPORT 8109

COMPETITIVE PATHWAYS IN CHLORINE DIOXIDE OXIDATION OF AMINES: AMIDE FORMATION FROM ACYCLIC AMINES

ELIZABETH P. BURROWS, Ph.D.

DAVID H. ROSENBLATT, Ph.D.

U S ARMY MEDICAL BIOENGINEERING RESEARCH & DEVELOPMENT LABORATORY

Fort Detrick

Frederick, Maryland 21701

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Treatment of dibenzylamine (1) and ethyl N,N-dibenzylglycinate (2) with chlorine dioxide (ClO_2) gave, in addition to the expected products of oxidative dealkylation, substantial amounts of amides. With 2 and preformed ClO_2 at pH 4-7, ethyl N,N-dibenzyloxamate (4) was the predominant isomer; however, with ClO_2 generated in situ at pH 2.5-3, ethyl N-benzoyl-N-benzyl glycinate (3) was predominant. In the latter case the combined yield of amides was sufficiently high (80%) to be of synthetic utility.

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INTRODUCTION

Chlorine dioxide (ClO_2) is well known to react with aliphatic amines to give products of oxidative dealkylation or, in the presence of a β-hetero atom, oxidative fragmentation.[1] In most cases a single mechanism, involving rate determining formation of an aminium cation radical, is operative.[1] m- and p-Substituted benzyldimethylamines are unexceptional;[2] however, with benzyl-t-butylamine and dibenzylamine, α-hydrogen abstraction competes with electron abstraction, and with benzylamine it is the predominant rate-determining process.[3] Kinetic studies had been carried out under pseudo-first order conditions with a large excess of amine at controlled pHs (range 6 to 9), and product analyses were done following reaction of ClO_2 with excess or stoichiometric equivalents of amine. Under these conditions only cleavage products were found.[1-3]

We sought to study the effects of ClO_2 in excess on certain amines in dilute aqueous mixtures, under conditions chosen to further our understanding of the chemistry of ClO_2 when used as a water disinfectant.

MATERIALS AND METHODS

A Hewlett Packard Model 5985B gas chromatograph/mass spectrometer/data system (GC/MS/DS) equipped with a 180 x 0.2 cm glass column packed with 3 percent OV-1 on Gas Chrom Q was used for product analyses. GC conditions generally were 80° for 1 min, then ΔT 15°/min to 240°. Mixtures containing primarily amides **4** and **5** were more conveniently analyzed at 200° for 1 or 2 min followed by the same programming to 240°. High resolution mass spectra were performed by the Middle Atlantic Mass Spectrometry Laboratory, The Johns Hopkins University School of Medicine, Baltimore, MD. TLC separations were performed on Merck silica gel F-254 plates (0.25 mm thickness) with 1:1 hexane-ether as eluant. The melting point (uncorrected) was determined on a Thomas-Hoover capillary apparatus. The ClO_2 solution (0.017 M) was prepared from reagent grade potassium persulfate and sodium chlorite.[4]

GENERAL PROCEDURE FOR CHLORINE DIOXIDE OXIDATIONS

Solutions of dibenzylamine (**1**, 1×10^{-2} mmol or ethyl N,N-dibenzylglycinate[5] (**2**, 5×10^{-3} mmol) in acetonitrile (2.5 mL) and ClO_2 (2 mL of the 0.017 M solution in 0.5 mL of 0.1 M phosphate buffer, pH 6.8) were mixed and allowed to stand 1 to 2 hr. For experiments at lower pH, dilute $HClO_4$ was added dropwise to the buffered ClO_2 solution before mixing. After reaction, the mixtures were saturated with NaCl and, if necessary, adjusted to near neutrality before extraction with CH_2Cl_2. The dried CH_2Cl_2 extracts were evaporated to dryness without heating, and the residues were dissolved in acetone for analysis by GC/MS. The results of typical runs are summarized in Table 1.

Table 1. Products of the Reaction of Acyclic Amines with Excess ClO_2 at pH 6.8

	PhCHO	$PhCH_2NH_2$	1	$PhCH{=}NCH_2Ph$	$(HO)_2CHCO_2Et$[a]	Amides 3	4	5	Others
1[b]	trace	4	38[c]	27	--	16	--	--	15
1[d]	9	12	16[c]	25	--	24	--	--	14
2[b]	trace	0	23	12	27	5	21	4	8

a. Identified on the basis of its mass spectrum.
b One hr.
c. Starting material.
d. Two hr.

ETHYL N,N-DIBENZYLOXAMATE (4) AND ETHYL N-BENZOYL-N-BENZYLGLYCINATE (5) FORMED WITH IN SITU GENERATED ClO_2

A mixture of 2 (38 mg, 0.132 mmol), 0.16 M $NaClO_2$ (50 mL), 0.08 M NaOCl (50 mL), and 1 M $HClO_4$ (4.7 mL) had pH 2.6. It was stirred 1.5 hr, then adjusted to pH 6 with dilute KOH and saturated with NaCl before extraction with two portions of CH_2Cl_2. The organic products (37 mg) were analyzed by GC/MS (shown in Figure 1) before separation and isolation of the two major amides by preparative TLC. High resolution mass spectra: calcd for $C_{18}H_{19}NO_3$ 297.1360; found for 4 297.1369; found for 5 297.1363. Characteristics of 4: mp 81-82°; m/e (relative intensity) 297 (1.5), 206 (97), 132 (21), 91 (100). Characteristics of 5: colorless syrup; m/e (relative intensity) 297 (1.2), 192 (90), 105 (100), 91 (23), 77 (29). Principal fragments in the low resolution mass spectra of 4 and 5 are shown structurally in Figures 2 and 3, and complete tabulations are given.

RESULTS AND DISCUSSION

We have shown that, for two acyclic amines having active α-methylene groups, reaction with ClO_2 in excess leads to a significant amount of amide formation in competition with oxidative dealkylation. Thus, N-benzoylbenzylamine (3) constituted 25 to 30 percent of the products of the relatively unreactive dibenzylamine (1). For the case of ethyl N,N-dibenzylglycinate (2), where two different α-methylene groups may compete in formation of isomeric amides, we studied its reaction with excess ClO_2 under different conditions of pH and solvent. Over the pH range 4 to 7 in the optimum medium, 1:1 acetonitrile-water, product composition did not vary greatly, and amides constituted 20 to 30 percent of the products. Despite the 2:1 preponderance of benzyl to carboethoxymethylene, isomer 4 predominated over 5 by a factor of 3 to 5. Table 1 summarizes the results of a typical run. Below pH 4, 2 was consumed less readily and the yields of amides were ower, with 4 still predominant.

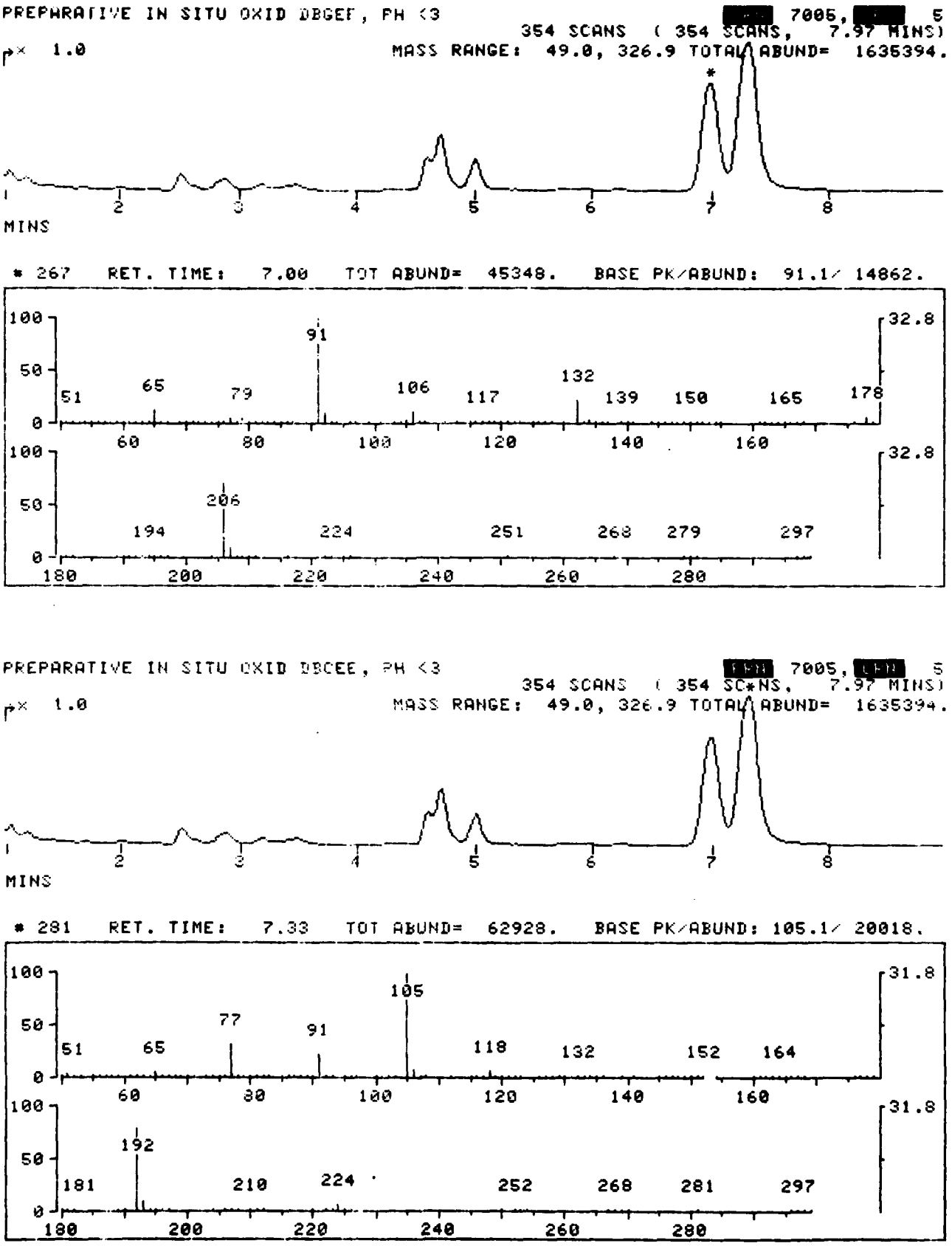

Figure 1. GC/MS Analysis of reaction products of ethyl N,N-dibenzylglycinate with ClO_2 generated in situ at pH 2.8.

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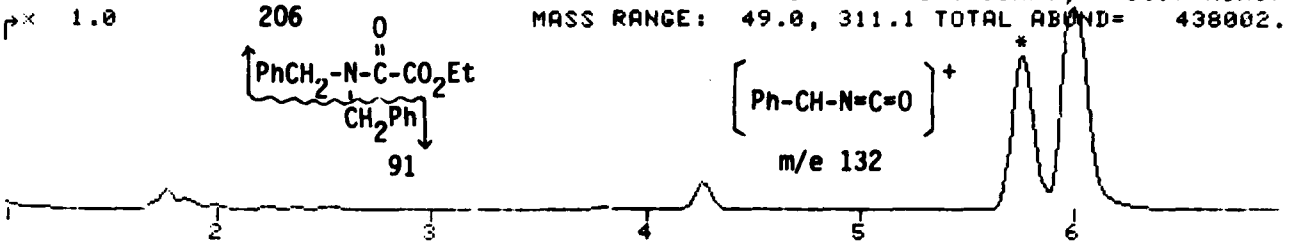
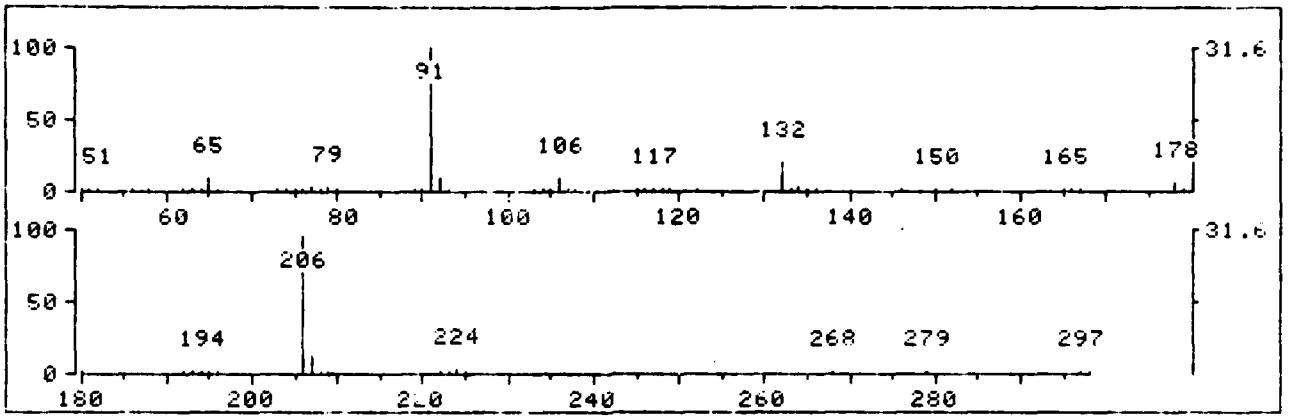
12 MAY 274 SCANS ; 274 SCANS, 5.97 MINS)
[illegible] 1.0 MASS RANGE: 49.0, 311.1 TOTAL ABUND= 438002.



* 219 RET. TIME: 5.77 TOT ABUND= 23170. BASE PK/ABUND: 91.1/ 7331.



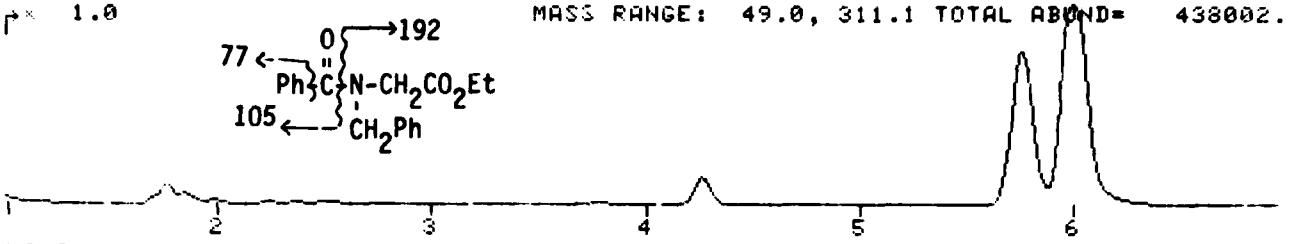
FRN 5019, SPECTRUM # 221 RET.TIME: 5.77, 66 PEAKS

M/Z	REL ABUND	M/Z	REL ABUND	M/Z	REL ABUND	M/Z	REL ABUND
50	.4	80	.3	122	.2	194	1.4
51	1.6	89	2.6	132	20.5	195	.5
52	.6	90	1.1	133	2.2	196	.5
56	.6	91	100.0	134	3.1	206	96.8
58	.1	92	9.7	135	.9	207	13.1
62	.2	93	.4	136	.2	208	1.6
63	1.5	103	.2	146	.2	209	.2
64	.4	104	2.1	150	.3	222	.1
65	9.8	105	2.2	152	.2	223	.2
66	.6	106	10.2	165	.6	224	3.8
73	.2	107	2.0	166	.2	225	.7
74	.2	108	.2	167	.4	268	.2
75	.3	115	.2	178	6.7	279	.2
76	.3	116	.3	179	.8	297	1.5
77	3.7	117	.6	180	.2	298	.4
78	1.3	118	.4	192	.2		
79	3.9	119	.3	193	.2		

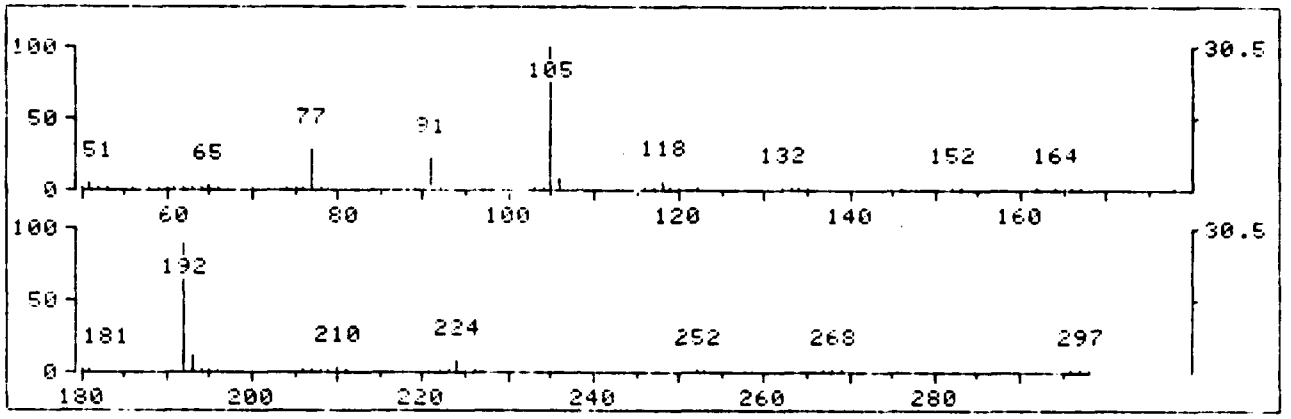
>PAUSE

Figure 2. Mass spectrum of ethyl N,N-dibenzyloxamate.

PREP IN SITU OXID DBGEE
12 MAY
274 SCANS (274 SCANS) 5.97 MINS
MASS RANGE: 49.0, 311.1 TOTAL ABUND= 438002.



230 RET. TIME: 6.02 TOT ABUND= 30541. BASE PK/ABUND: 105.1/ 9328.



FRN 5019, SPECTRUM # 232 RET.TIME: 6.02, 77 PEAKS

M/Z	REL ABUND	M/Z	REL ABUND	M/Z	REL ABUND	M/Z	REL ABUND
50	1.1	79	.4	134	.4	208	.2
51	4.9	88	.2	135	.3	209	.1
52	.5	89	1.4	146	.1	210	3.8
53	.1	90	.7	152	.3	211	.7
56	.2	91	22.7	153	.1	222	1.8
58	.2	92	2.1	162	.2	223	.5
59	.2	102	.1	164	1.5	224	8.2
60	.3	103	.2	165	.7	225	1.3
61	.2	104	1.2	166	.2	226	.1
62	.2	105	100.0	167	.3	252	2.5
63	.8	106	8.6	178	.2	253	.5
64	.4	107	.8	180	.1	267	.1
65	4.5	116	.2	181	.2	268	.4
66	.3	117	.8	192	89.5	269	.1
70	.1	118	6.5	193	12.0	296	.5
74	.3	119	1.0	194	1.4	297	1.2
75	.4	120	.2	195	.3	298	.3
76	1.3	122	.1	196	.1		
77	29.0	132	.8	206	1.5		
78	2.7	133	.1	207	.3		

>PAUSE

Figure 3. Mass spectrum of ethyl N-benzoyl-N-benzylglycinate.

While amide formation by ClO_2 has not been previously reported, the extent of competitive cleavage reactions under the above conditions precluded synthetic utility in these cases. However, treatment of **2** with ClO_2 generated in situ[6] from the reaction of chlorite and HOCl at pH 2.5-3 gave amides **4** and **5** in a combined yield of 80 percent, with **5** predominating (Scheme 1). These amides were readily separated by preparative TLC. At higher pH the in situ reaction was slower and the yields of amides were lower. It should be emphasized that HOCl alone at pH 2.8 gave only cleavage products, while chlorite alone was inert.

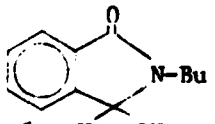
Scheme 1

$$(PhCH_2)_2NCH_2CO_2Et \xrightarrow[\text{pH 2.5-3}]{ClO_2^-,\ HOCl} PhC(=O)N(CH_2Ph)CH_2CO_2Et + (PhCH_2)_2NC(=O)CO_2Et + PhC(=O)NHCH_2Ph + \text{Others}$$

2 **5**, 50±5% **4**, 30±5% **3**, 5±3% 5±3%

CONCLUSIONS

Previously reported conversions of amine α-methylene groups to carbonyls have been generally limited to cyclic amines. For example, ruthenium tetroxide was useful for the oxidation of N-substituted pyrrolidines to amides, and in some cases further to imides.[7] N-Arylpyrrolidones were obtained on ozonation of N-arylpyrrolidines,[8] and air oxidation of N-butylisoindoline gave predominantly N-butylphthalimidine and N-butylphthalimide.[9] Some years prior to initiation of this work, N-butyl-3-hydroxyphthalimidine (**6**) had been observed in our laboratory as the major product of ClO_2 treatment of N-butylisoindoline.[10] We now anticipate that ClO_2 may be of general utility in the oxidation of active α-methylene groups in acyclic amines as well.



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In addition to this practical aspect, the observed predominance of amide **4** over **5** except in the in situ reaction at low pH may be of some mechanistic significance. In the reactions of preformed ClO_2, loss of the more acidic proton from the initial aminium cation radical[11] appears to be the preferred process, whereas in the in situ case at low pH, direct abstraction of the α-hydrogen to give the more stable radical (benzyl vs. glycine α-carbon) may be favored. Thus the possibility of a difference in mechanism with the two reagents, preformed and in situ generated, suggested earlier by the observation of different ratios of cleavage products from benzyldimethylamines in the two cases,[2] remains to be investigated.

While neither ClO_2 in acetonitrile-water mixtures or the aqueous in situ conditions at low pH duplicates water disinfection conditions, the possible presen. . of ami' in amine-containing waters after ClO_2 treatment must now be conside... in sessment of hazards.

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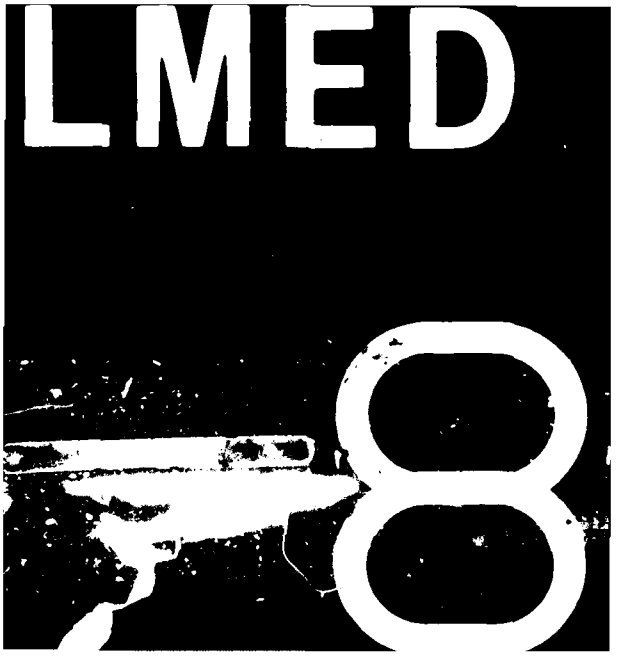
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